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09/935,386	08/22/2001	John C. Yu	TSRI 753.1	1866

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	7

DATE MAILED: 08/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/935,386	YU, JOHN C.	
	Examiner	Art Unit	
	Thai-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-17 are pending and under current examination.

Information Disclosure Statement

The Information Disclosure Statements, filed 1/18/02 [Paper No. 4] and 9/10/02 [Paper No. 6] have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 17, as written, are vague and indefinite. The claims recite that the rodent is maintained for "from about 5 to 10 days" see part (b) of the claim. The term "from about" is not defined by the claims, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Claims 2-10 depend from claim 1.

Claim 1, as written, is unclear because step (c), injecting a rodent with an effective engrafting amount of primary human leukemia cells, fails to relate to the preamble, a process for making an *in vivo* model of human leukemia. For example, the engrafted cells would need to recapitulate symptoms leukemia, and be engrafted

for a certain period of time in order to produce such symptoms. Claims 2-10 depend from claim 1.

Claim 4, as written, is vague and indefinite. The claim recites that the sub-lethal dose of irradiation is "about" 350 rads. However, the term "about" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 5, as written, is vague and indefinite. The claim recites that the effective engrafting amount of primary human leukemia cells is from "about" 10^6 to "about" 10^7 cells. The term "about" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 7, as written, is vague and indefinite. The claim recites that the effective pre-conditioning amount of human fetal cord blood mononuclear cells is from "about" 10^6 to "about" 10^8 cells. The term "about" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim 12, as written, is unclear. The claim recites that *the* leukemia-initiating cell is maintained within the leukemia engrafted rodent. This is unclear

because it would be expected that the rodent would have more than one leukemia-initiating cells. Claims 13 and 14 depend from claim 12.

Claim 17, as written, is unclear because step (c), injecting a rodent with an effective engrafting amount of primary human leukemia cells, fails to relate to the preamble, a process for making an *in vivo* model of human leukemia. For example, the engrafted cells would need to recapitulate symptoms leukemia, and be engrafted for a certain period of time in order to produce such symptoms.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 10-16 rejected under 35 U.S.C. 102(b) as being anticipated by Blair *et al.* [Blood, 89:3104-3112 (1997)].

The claims are directed to an immunodeficient rodent having engrafted human leukemia cells, wherein the leukemia-initiating cell is maintained within the leukemia-engrafted rodent, wherein the rodent is a NOD/scid mouse, wherein the rodent is irradiate, injected with human fetal cord blood mononuclear cells and then injected with human primary leukemia cells, wherein the engrafted leukemia cells are found in the bone marrow and spleen of the rodent.

Note that certain claims are product-by-process claims (see claims 10 and 15, for example). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Blair teach the engraftment of human acute myeloid leukemia (AML) cells in NOD/scid mice. See Abstract. They teach that the NOD/scid mice were first irradiated and then injected intravenously with AML cells. See Material and Methods, p. 3105, 2nd column, last ¶. Blair teach the cytogenetic analysis of the

transplanted cells, wherein it was found that the engrafted cells were expressed in the bone marrow and the spleen of the mice. See p. 3109, 1st column, and Table 4.

Accordingly, Blair anticipates the claimed invention.

Claims 10-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Steele [**Blood**, 90:2015-2019 (1997), Reference #5 on IDS filed 9/10/02].

The claims are directed to an immunodeficient mouse having engrafted human leukemia cells, wherein the mouse is a NOD/scid mouse, and the engrafted leukemia cells are found in the bone marrow and spleen of the mouse. Note that claims 10 and 15 are product-by-process claims, *see supra*.

Steele teach the engraftment of human leukemia cells into SCID and NOD/SCID mice and the mice were then analyzed. The spleen and bone marrow collected from the mice were analyzed by flow cytometry using a panel of monoclonal antibodies to human leukocyte cell surface markers to establish the extent to which the primary human immunophenotype was retained in the mice. See pp. 2015-2016, Materials and Methods, and Table 2.

Accordingly, Steele anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blair *et al.* [Blood, 89:3104-3112 (1997)] when taken with Haynesworth [U.S. Pat. No. 5,733,542, Reference #1 on IDS filed 9/10/02] in further view of Caplan [U.S. Pat. No. 5,486,359, published January 23, 1999].

The claims are directed to *in vivo* models of human leukemia and methods of producing an *in vivo* model of human leukemia by pre-conditioning an immunodeficient rodent by administering a sub-lethal dose of irradiation, injecting the rodent with an effective pre-conditioning amount of mononuclear cells derived from human fetal cord blood, maintaining the rodent for 5-10 days, injecting the rodent with an effective engrafting amount of primary human leukemia cells. In further embodiments, the immunodeficient rodent is a NOD/scid mouse, the sub-lethal dose of irradiation is accomplished by irradiating the rodent with about 350 rads of total body gamma radiation, the effective pre-conditioning amount of human fetal cord mononuclear cells is from about 10^6 to 10^8 cells and the mononuclear stem cells comprise mesenchymal stem cells.

Blair teach the engraftment of human acute myeloid leukemia (AML) cells in NOD/scid mice. See Abstract. They teach that the NOD/scid mice were first irradiated at 4 Gy γ and then 24 hours later injected intravenously with 10^6 AML

cells/ml. See Material and Methods, p. 3105, 2nd column. Blair teach the cytogenetic analysis of the transplanted cells, wherein it was found that the engrafted cells were expressed in the bone marrow and the spleen of the mice. See p. 3109, 1st column, and Table 4.

Blair differ from the claimed invention in that they do not teach the pre-conditioning of the immunodeficient rodent by injecting the rodent with an effective pre-conditioning amount of mononuclear cells derived from human fetal cord blood, wherein the cells are mesenchymal stem cells. However, prior to the time the claimed invention was made, Haynesworth teach methods for enhancing bone marrow engraftment by administration of mesenchymal stem cells. In particular, Haynesworth teach that after lethal doses of radiation, culture-expanded MSCs can increase survival and decrease the time of blood and marrow regeneration [see col. 1, lines 40-49]. Haynesworth teaches that the amount of MSC preparation is at least $1x10^4$ cells per kg of body weight, and not more than $7x10^5$ MSC/kg and that the MSCs may be administered prior to the graft introduction for at least 7 days [see col. 3-4, bridging ¶]. They teach that the mesenchymal stem cells that would be used to enhance the engraftment can come from any source [see col. 1, lines 30-35]. Haynesworth differs from the claimed invention in that they do not teach MSCs isolated from human fetal cord blood. However, prior to the time the claimed invention was made, Caplan teach the isolation and purification of human

mesenchymal stem cells, which can be obtained from such sources as umbilical cord [see col. 2, line 20].

Accordingly, in view of the combined teachings of Blair, Haynesworth and Caplan, it would have been obvious for one of ordinary skill in the art to modify the mouse model, as taught by Blair, by pre-conditioning the mouse with mesenchymal stem cells obtained from human fetal cord blood, as taught by Haynesworth and Caplan, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as the administration of MSCs enhance engraftment of cells, as supported by Haynesworth [see col. 1, lines 50-67].

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Claims 1, 2, 4-9 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Steele *et al.* [Blood 86:782A (1995)] when taken with when taken with Haynesworth [U.S. Pat. No. 5,733,542, Reference #1 on IDS filed 9/10/02] in further view of Caplan [U.S. Pat. No. 5,486,359, published January 23, 1999].

Steele teaches that SCID mice were irradiated [2Gy] and then injected intravenously with 1-2 x 10^7 human T-cell acute lymphoblastic leukemia (T-ALL) cells. The mice were then analyzed and it was found that the cells were expressed

in the spleen and bone marrow. Steele differs from the claimed invention in that they do not teach the pre-conditioning of the immunodeficient rodent by injecting the rodent with an effective pre-conditioning amount of mononuclear cells derived from human fetal cord blood, wherein the cells are mesenchymal stem cells.

However, prior to the time the claimed invention was made, Haynesworth teach methods for enhancing bone marrow engraftment by administration of mesenchymal stem cells. In particular, Haynesworth teach that after lethal doses of radiation, culture-expanded MSCs can increase survival and decrease the time of blood and marrow regeneration [see col. 1, lines 40-49]. Haynesworth teaches that the amount of MSC preparation is at least $1x10^4$ cells per Kg of body weight, and not more than $7x10^5$ MSC/kg and that the MSCs may be administered prior to the graft introduction for at least 7 days [see col. 3-4, bridging ¶]. They teach that the mesenchymal stem cells that would be used to enhancing the engraftment can come from any source [see col. 1, lines 30-35]. Haynesworth differs from the claimed invention in that they do not teach MSCs isolated from human fetal cord blood. However, prior to the time the claimed invention was made, Caplan teach the isolation and purification of human mesenchymal stem cells, which can be obtained from such sources as umbilical cord [see col. 2, line 20].

Accordingly, in view of the combined teachings of Steele, Haynesworth and Caplan, it would have been obvious for one of ordinary skill in the art to modify the mouse model, as taught by Steele, by pre-conditioning the mouse with mesenchymal

stem cells obtained from human fetal cord blood, as taught by Haynesworth and Caplan, with a reasonable expectation of success. One of ordinary skill in the art would have been sufficiently motivated to make such a modification, as the administration of MSCs enhance engraftment of cells by increasing the survival and decrease the time of blood and marrow regeneration, as supported by Haynesworth [see col. 1, lines 50-67].

Thus the claimed invention as a whole was clearly *prima facie* obvious at the time the claimed invention was made especially in the absence of sufficient, clear and convincing evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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